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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,685	06/29/2001	Rene Bruno	P23,565-A US	8546

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EXAMINER	
NICKOL, GARY B	
ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 02/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/869,685	BRUNO, RENE	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *6-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The Election filed November 22, 2002 (Paper No. 7) in response to the Office Action of September 10, 2002 is acknowledged and has been entered.

Claim 30 was added with the amendment filed on 1/03/03 (Paper No. 8).

Claims 1-30 are pending.

Claims 6-29 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 1-5, 30 are currently under prosecution.

The species election between breast, ovarian, lung, and non-small cell lung cancer is withdrawn. A species election requirement however remains in effect between cancers of the head and neck, gastric cancer, pancreatic cancer, melanomas, and soft tissue sarcomas.

Applicant's election with traverse of Group 1, claims 1-5 in Paper No 7 is acknowledged. The traversal is on the ground(s) that the inventions have not been shown to be independent and the examination of all groups would not impose a serious burden on the examiner. Applicants further point to MPEP 803. These arguments have been considered but are not found persuasive as such arguments do not apply when restriction is required under 35 USC 121 and 372, as in the instantly filed application. Thus, when the Office considers international applications as an International Searching Authority, as an International Preliminary Examining Authority, and during the national stage as a Designated or Elected Office under 35 U.S.C. 371, PCT Rule 13.1

and 13.2 will be followed when considering unity of invention of claims of different categories without regard to the practice in national applications filed under 35 U.S.C. 111.

Applicants further argue that the examiner has ignored the provision of PCT Rule 13.2 regarding a technical relationship among inventions involving one or more of the same or corresponding special technical features. Applicants argue that claims of Groups 1-3 contain more than one of the same or corresponding special technical features. This argument has been considered but is not found persuasive. Here, the inventions of the various groups comprise special technical features that do not relate to a general inventive concept under PCT Rule 13.1 for the reasons set forth in Paper No. 7. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruno *et al.* (Cancer Surveys, Vol. 17, pages 305-313, 1993) and Urien *et al.* (Invest. New Drugs, Vol.14, pages 147-151, 1996, IDS).

The claims are drawn to a method of determining the dosage of a taxoid to administer to a patient who is being treated for cancer whose body fluids include alpha-1-acid glycoprotein

comprising observing the patient's level of alpha-1-acid glycoprotein; evaluating said level to determine the dosage of the taxoid to administer to the patient by comparing said level to a predetermined alpha-1-acid glycoprotein level derived from a population of patients having said cancer and treated with said taxoid at a common dosage; and based on said evaluation, recommending the dosage of the taxoid to administer to the patient (Claim 1); wherein said taxoid is selected from the group consisting of docetaxel and paclitaxel (Claim 2); wherein said cancer is selected from the group consisting of breast, ovarian, lung, and non-small cell lung cancers (Claims 3-5, 30).

Bruno *et al.* teach that the safety, efficacy, and pharmacokinectics of Taxotere (docetaxel) have been investigated for a variety of schedules in six phase I studies conducted in Europe and the United States and that objective responses have been observed in ovarian carcinoma, breast carcinoma, small cell and non-small cell lung cancers (page 308, 1st paragraph). Bruno *et al.* further teach that in examining pooled data from two different populations of patients receiving short intravenous infusion of docetaxel (see Table 1, page 310), the pharmacokinetic outcome (CL) was independent of the dose and formulation; however patient factors such as body surface area and age explained some interpatient variability in CL (page 310).

Bruno *et al.* do not mention that levels of alpha-1-acid glycoprotein should be observed/measured in order to determine the dosage of a taxoid to administer to a patient who is being treated for cancer.

Urien *et al.* teach that lipoproteins, alpha-1-acid glycoprotein, and albumin were the main carriers of docetaxel in plasma, and owing to the high interindividual variability of alpha-1-acid

glycoprotein plasma concentration, particularly in cancer, it was concluded that alpha-1-acid glycoprotein should be the **main determinant** of docetaxel plasma binding variability (abstract). From their simulations, Urien *et al.* predicted that when alpha-1-acid glycoprotein concentrations increased from 5 to 65uM, the docetaxel free fraction decreased from approximately 9 to 5%, i.e. "the serum free fraction of docatexel is divided by two" (page 150, 2nd column, 1st paragraph). Urien *et al.* further teach that docataxel clearance and also some effects were related to alpha-1-acid glycoprotein concentration in 577 patients wherein the higher the alpha-1-acid glycoprotein concentration, the lower the free plasma fraction and the clearance.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modulate the teachings of Bruno *et al.* so as to quantify the level of alpha-1-acid glycoprotein in those cancer patients treated with docetaxel. One would have been motivated to do so because Bruno *et al.* teach that the pharmacokinetic outcome (CL) of docetaxel was independent of the dose and formulation and suggest that there was some degree of interpatient variability, and Urien *et al.* recognize that a significant percentage of interpatient variability, especially in cancer patients, is due to serum concentrations of alpha-1-acid glycoprotein wherein the higher the alpha-1-acid glycoprotein concentration, the lower the free plasma fraction and the clearance. Moreover, Urein *et al.* concluded that alpha-1-acid glycoprotein should be the **main determinant** of docetaxel plasma binding variability.

Thus, having measured the amounts of alpha-1-acid glycoprotein in a population of cancer patients treated with docataxel, it would be obvious to use this data in order to determine the appropriate dosage of docatexl to be administered to cancer patients with variable (high or low) serum levels of alpha-1-acid glycoprotein. For example, a higher amount of serum alpha-1-

acid glycoprotein may require an increased dosage of docatexel in order to raise the plasma free fraction and clearance. Thus, when determining the dosage of a taxoid (i.e., docatexel) to be administered to a cancer patient, it would be obvious to one of ordinary skill in the art at the time the invention was made to observe the patient's level of alpha-1-acid glycoprotein and compare this amount to the pre-determined levels of alpha-1-acid glycoprotein observed in similar cancer patients having been treated with a common dosage of a taxoid so that one may derive an appropriate dosage for said patient.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
February 10, 2003